CAPRISA

CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

HIV Vaccines and BnAb Research

Past, present and future

HPRU Scientific Symposium

15 February 2021

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HIV VACCINE TRIALS NETWORK

NATIONAL INSTITUTES OF HEALTH

HPTN HIV Prevention Trials Network

NRF National Research Foundation

science & innovation Department: Science and Innovation REPUBLIC OF SOUTH AFRICA

saMRC advancinglife

health Department: Health REPUBLIC OF SOUTH AFRICA

Outline

- From CAPRISA with Love…
- HIV Vaccines past to present
- Broadly neutralizing antibody studies
- CAPRISA's BnAb programme
- Future Vaccine and BnAb concepts
- Conclusions

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CAPRISA's Leadership and Facilities

Headquarters

Clinical research facilities

DDMRI

eThekwini

Vulindlela

Springfield

Umlazi

www.caprisa.org

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CAPRISA's goal & affiliations

Goal: To undertake ***globally relevant & locally responsive*** research that contributes to understanding HIV pathogenesis, prevention & epidemiology as well as TB-HIV treatment

science & innovation
Department:
Science and Innovation
REPUBLIC OF SOUTH AFRICA

CAPRISA hosts a DSI-NRF Centre of Excellence in HIV Prevention

NRF National Research Foundation

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

CAPRISA hosts a MRC HIV-TB Pathogenesis and Treatment Research Unit

CAPRISA hosts a DoH-MRC Special Initiative for HIV Prevention Technology

saMRC advancinglife

UNAIDS

CAPRISA is the UNAIDS Collaborating Centre for HIV Research and Policy

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From CAPRISA with Love…

Joint projects and opportunities

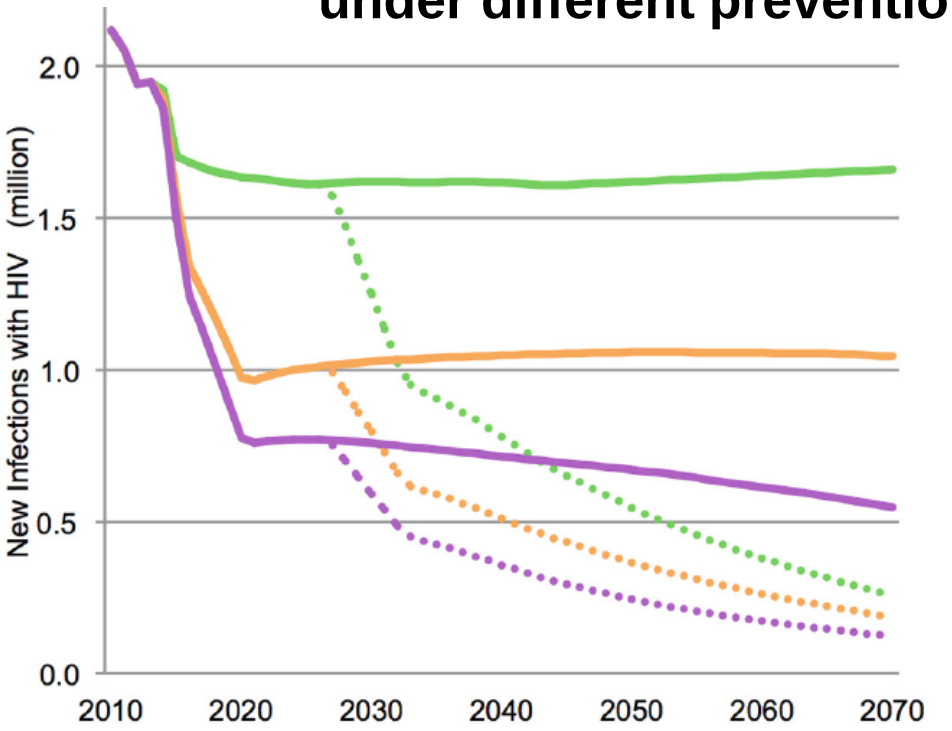
- **Improving HIV and STI care with point of care testing**
  - Andy Gibbs and Beth Spooner
- **Making an impact on TB and MDR-TB**
  - Marion Loveday and Nesri Padayatchi
- **ENSEMBLE COVID-19 Trial**
  - 5 trial sites
- **SISONKE Phase 3b JnJ vaccine implementation study**
  - National and Regional leadership

Advancing STI Care in SA

Potential impact of an HIV vaccine

1.7 million people became newly infected with HIV in 2018

Reduction of new HIV infections with & without a vaccine under different prevention scale-up scenarios



Vaccine efficacy	HIV infections averted (2027–2070)
30%	8.4 million
40%	10.6 million
50%	12.6 million
60%	14.5 million
70%	16.1 million
80%	17.7 million
90%	19.0 million

- **Assumptions**: Vaccine introduction in 2027, 50% coverage, 70% efficacy
- **IFE** = UNAIDS' Investment Framework Enhanced includes scale-up of PrEP, TasP, and other prevention methods

Harmon, et al. PLOS One. 2016

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History of HIV Vaccine Research

- 1983: HIV discovered
- 1984: U.S. government announced AIDS vaccine programme.
- 1987: First HIV vaccine clinical trial at the NIH
- 1998: VaxGen initiated Phase 3 trial of AIDSVAX (VAX004) in North America/ Netherlands with 5,400 volunteers followed by AIDSVAX (VAX003) involving 2,500 volunteers in Thailand.
- 2000: NIH forms HVTN
- 2003: The U.S. and Royal Thai governments initiate RV144, a Phase 3 ‘prime-boost’ trial (ALVAC-AIDSVAX B/E)
- 2007: Step and Phambili trials (human Ad5 vector expressing 3 HIV proteins) halted due to safety concerns and later on due to lack of efficacy.
- 2009: RV144 reveals modest preventive effect in humans.
- 2010: The Pox-Protein Public-Private Partnership (P5) formed to build on RV144.

F Laher, L-G Bekker, N Garrett, EM Lazarus & GE Gray. Review of preventative HIV vaccine clinical trials in South Africa. Archives of Virology volume 165, pages2439–2452(2020)

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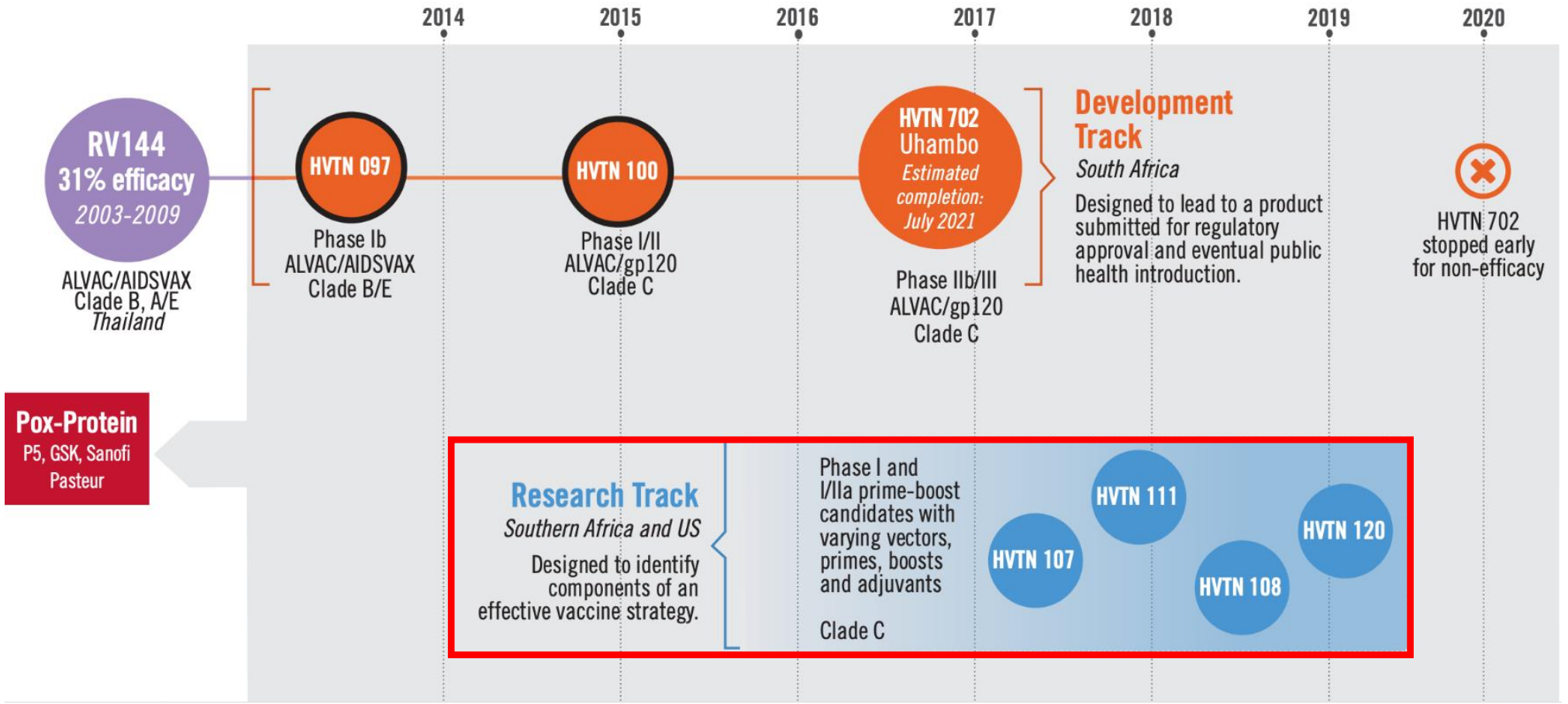
Pox-Protein Public Private Partnership (P5) Studies



Designed to investigate different:

- prime-boost regimens (DNA or ALVAC prime +/- protein co-administration)
- protein doses
- adjuvants (MF59, $AS01_B$ and alum) or no adjuvant
- delivery methods (needle & syringe versus Biojector®)

HVTN 702: The Journey of Hope

SOUTH AFRICA

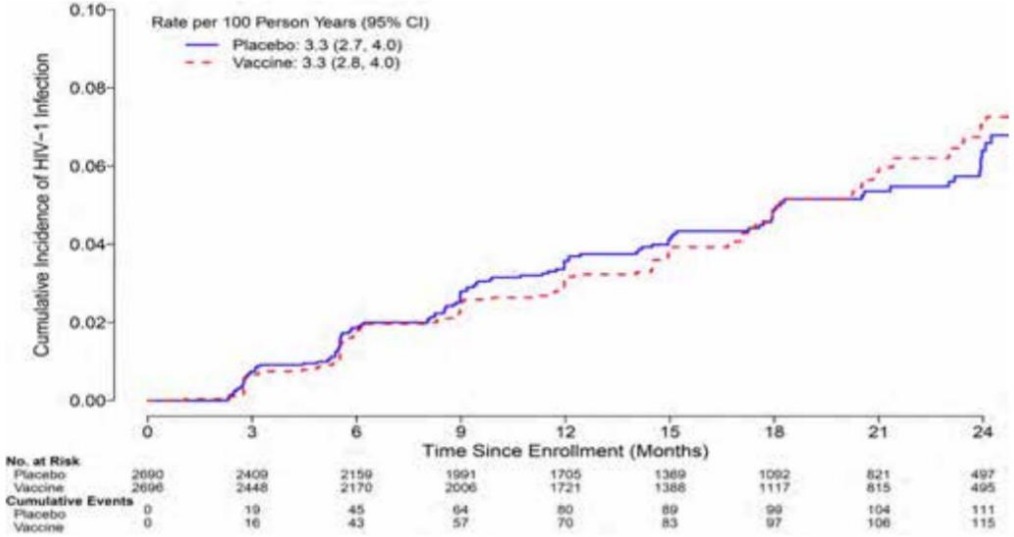
Biggest HIV vaccine trial halted after early results show it fails to protect against infection

Times LIVE

uhambo

A JOURNEY OF HOPE TO PREVENT HIV

- Started Oct 2016
- Fully enrolled: **N=5407**
- No safety concerns
- Interim analysis: No efficacy



Group	N	Primary vaccine regimen				Booster	
		M0	M1	M3	M6	M12	M18
1	2700	ALVAC-HIV (vCP2438)	ALVAC-HIV	ALVAC-HIV + bivalent subtype C gp120/ MF59	ALVAC-HIV + bivalent C gp120/ MF59	ALVAC-HIV + bivalent C gp120/ MF59	ALVAC-HIV + bivalent C gp120/ MF59
2	2700	Placebo					

HVTN 108 Study Design

Groups

Priming with DNA

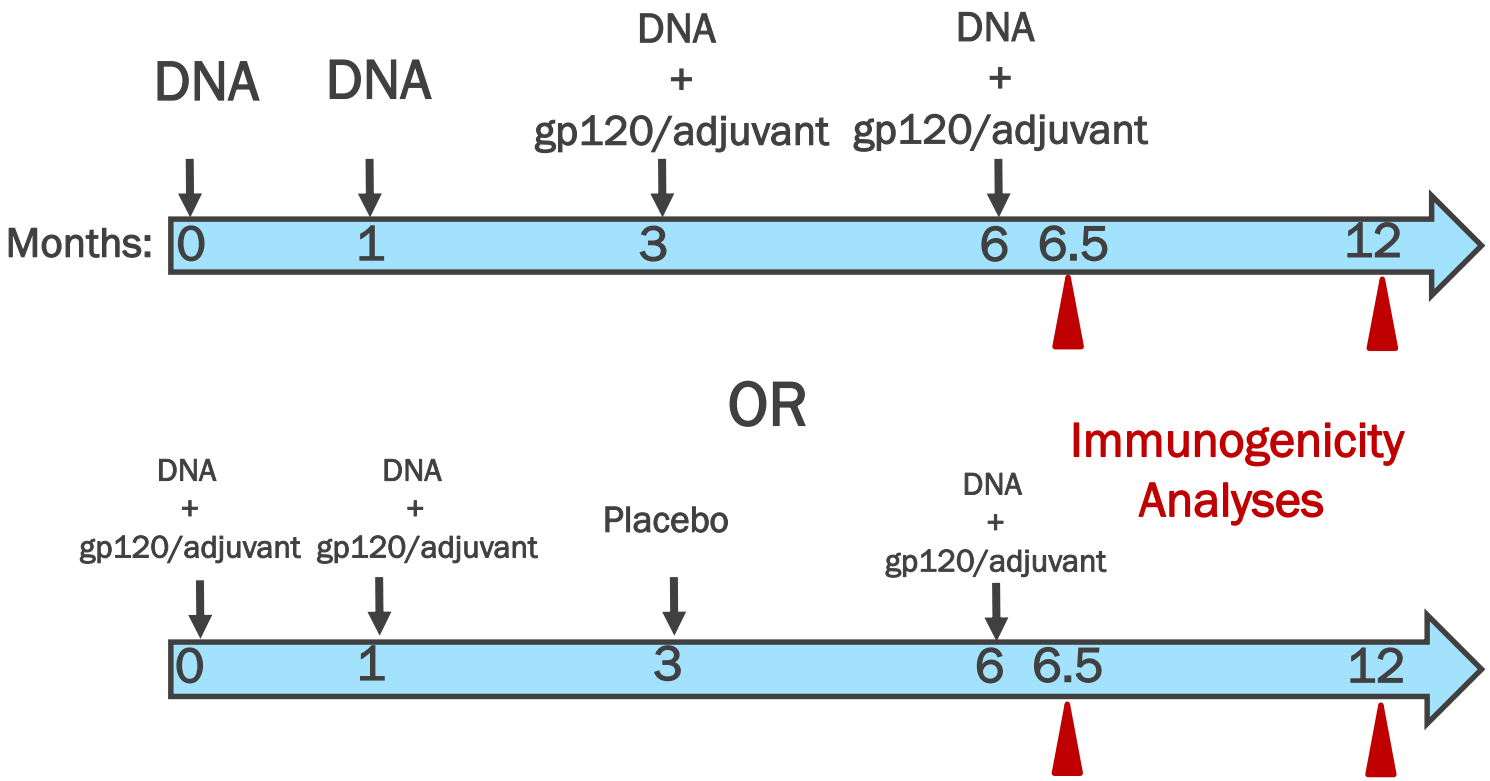
- T1: MF59- 100µg protein
- T2: $AS01_B$-100µg protein
- T3: $AS01_B$- 20µg protein

Co-admin with DNA

- T4: MF59 -100µg protein
- T5: $AS01_B$- 100µg protein
- T6: $AS01_B$- 20µg protein

No DNA

- T7: $AS01_B$- 20µg protein
- P1: Placebo



Comparisons

1. Adjuvants
   MF59 vs $AS01_B$
2. High vs. low dose Env gp120 protein with $AS01_B$
3. DNA prime-protein boost vs. co-administration vs. protein only (TBD)

Study Products

DNA-HIV-PT123: ZM96 *env* gp140, *gag* and *nef*
Protein: bivalent subtype C Env gp120 (20 µg or 100 µg each of TV1.C and 1086.C)
Adjuvant: MF59 or $AS01_B$

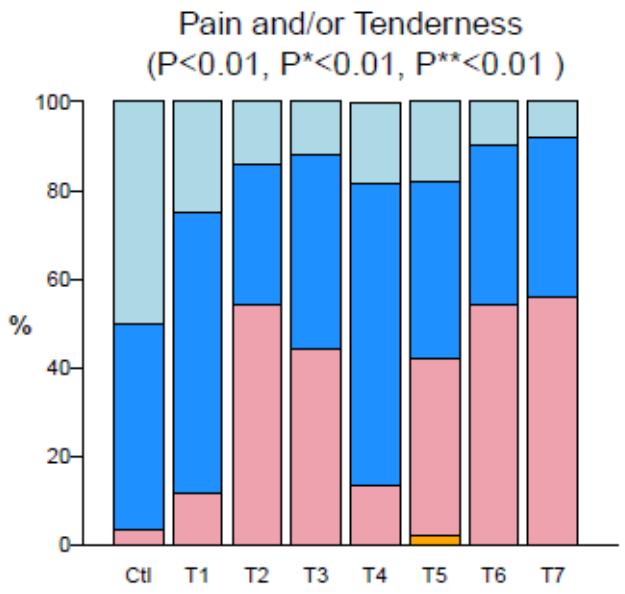
Safety Summary

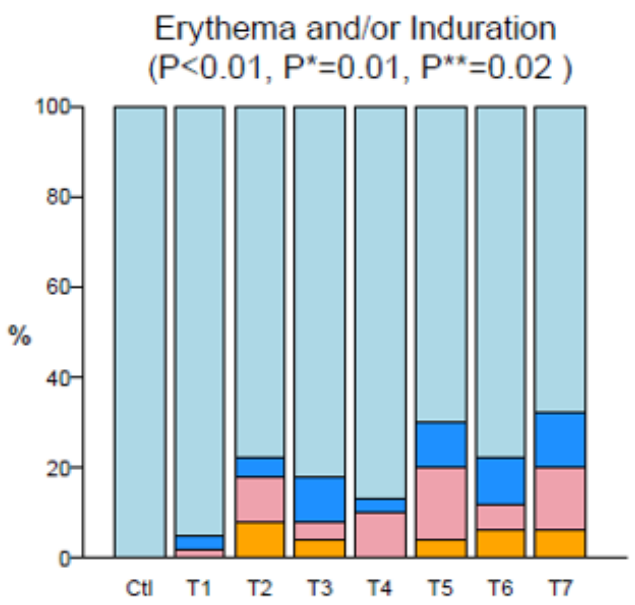
Maximum local reactogenicity events higher in $AS01_B$ than MF59 regimen

T1: PB@ 100 w/MF59
T2: PB@ 100 w/AS01b

T3: PB@ 20 w/AS01b
T4: CA@ 100 w/MF59
T5: CA@ 100 w/AS01b

T6: CA@ 20 w/AS01b
T7: P@ 20 w/AS01b



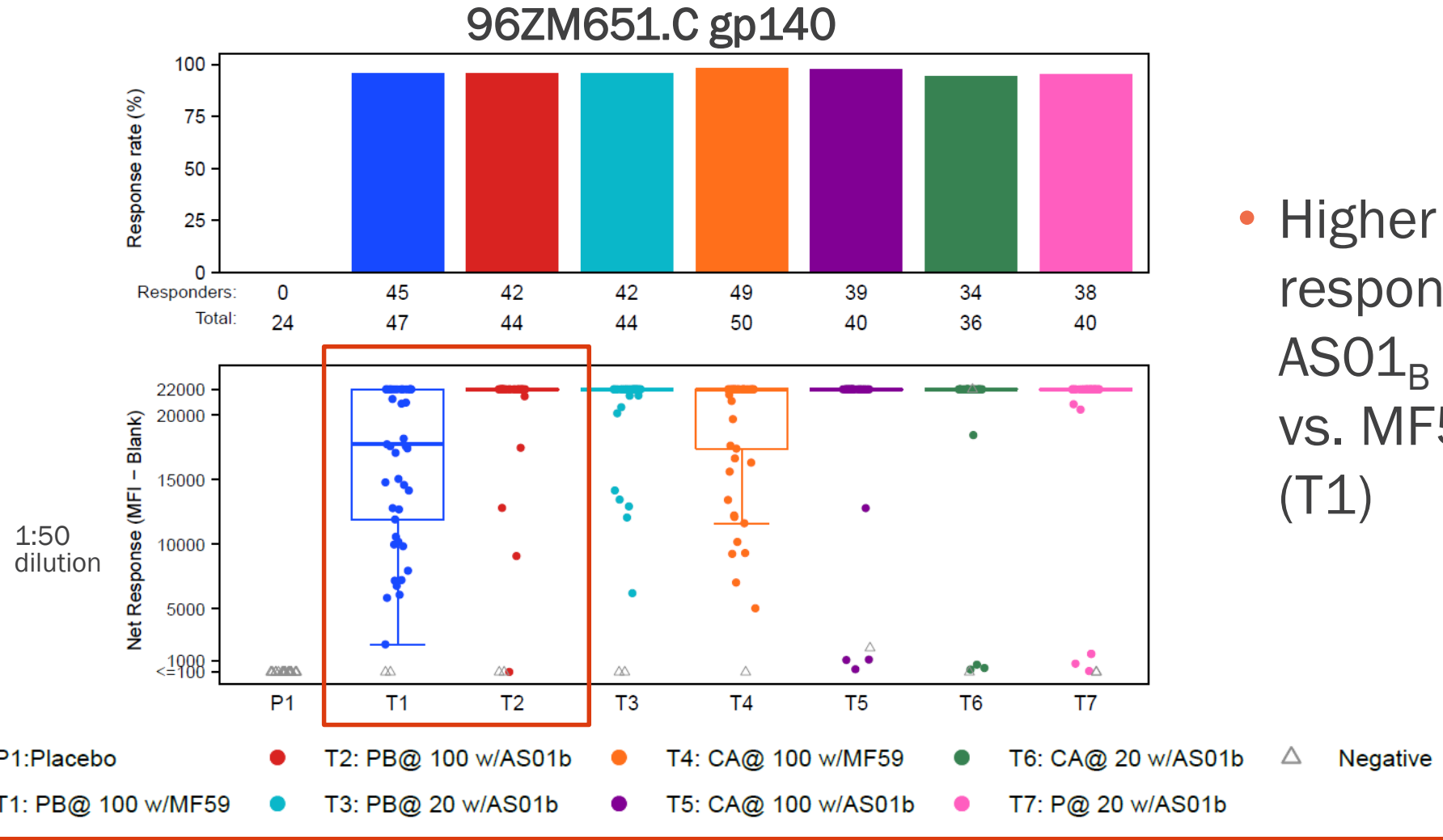


P: Across treatment arms; P*: T1 vs T2/3; P**: T4 vs T5/T6/T7

- No clinically significant differences in AEs or SAEs between groups.
- 3.6% of participants discontinued vaccinations due to reactogenicity events
- Most severe events at US sites

Gr 4: Complications | Gr 3: Severe | Gr 2: Moderate | Gr 1: Mild | None/Not Gradable

High HIV-specific IgG response rate and magnitude to clade C Env (prime sequence) across groups at 6.5M

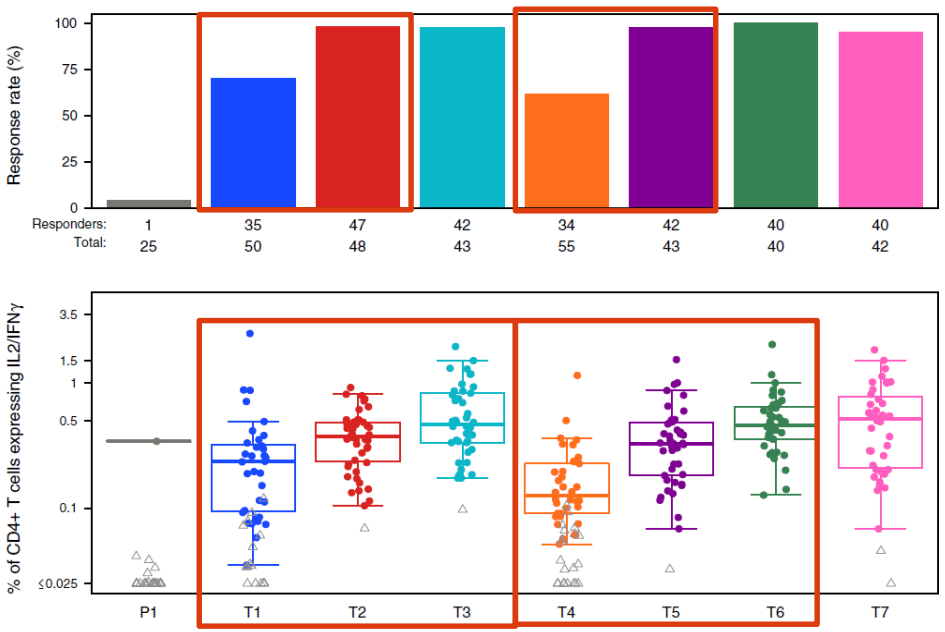


- Higher magnitude responses in $AS01_B$ group (T2) vs. MF59 group (T1)

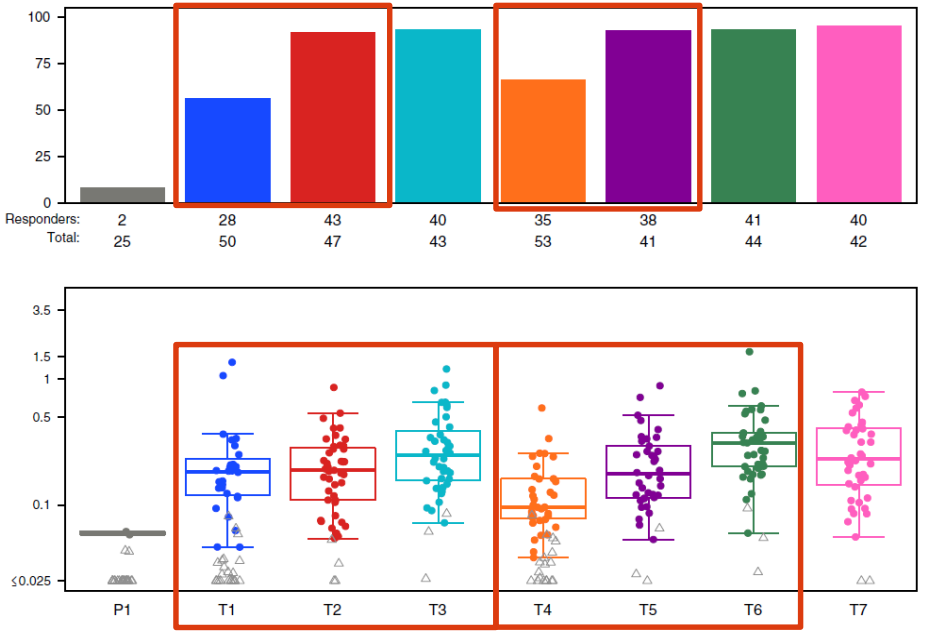
Statistically significant difference

CD4+ T-cell response rates and magnitude to Any Env* higher in the AS01$_B$- than MF59-adjuvanted regimens at 6.5M & 12M

Month 6.5



Month 12



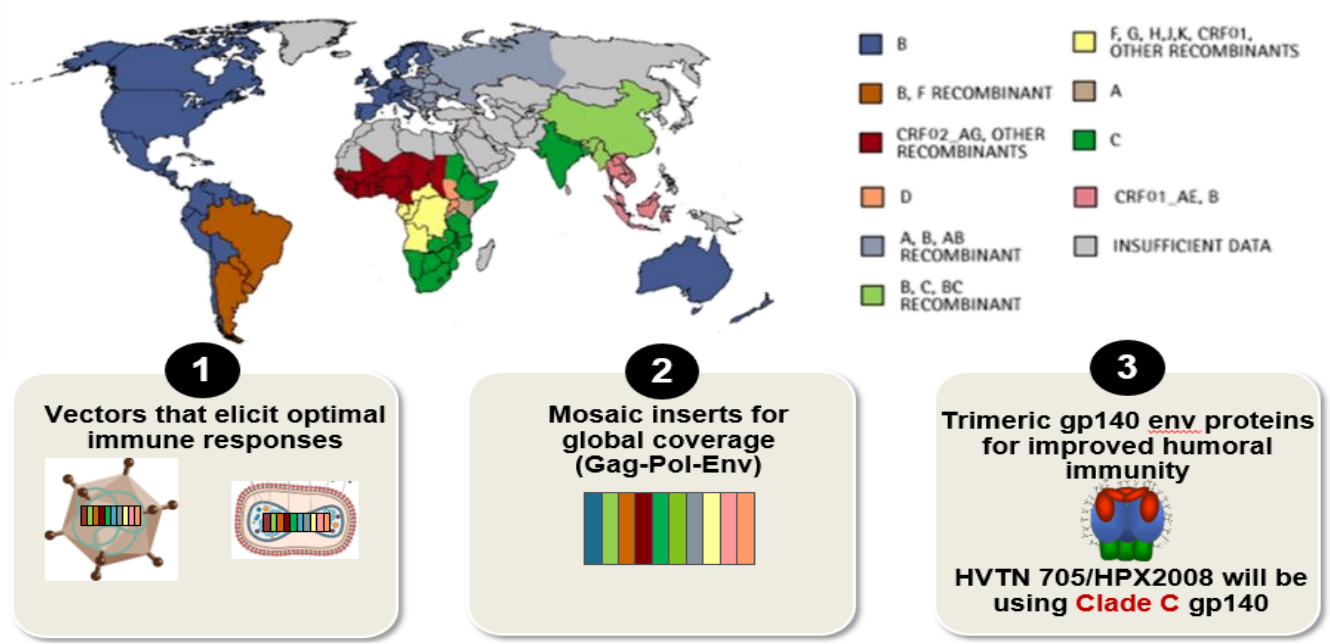
Low dose protein elicited higher magnitude responses than high dose.

- P1:Placebo
- T1: PB@ 100 w/MF59
- T2: PB@ 100 w/AS01b
- T3: PB@ 20 w/AS01b
- T4: CA@ 100 w/MF59
- T5: CA@ 100 w/AS01b
- T6: CA@ 20 w/AS01b
- T7: P@ 20 w/AS01b
- Negative

*ANY ENV defined as max of 1086 gp120, TV1 gp120 and Env ZM96.

HVTN 705/HPX 2008 Mosaic Vaccine Trial

Phase 2b trial of Ad26.Mos4.HIV & alum-adjuvanted clade C gp140 to prevent HIV in African women

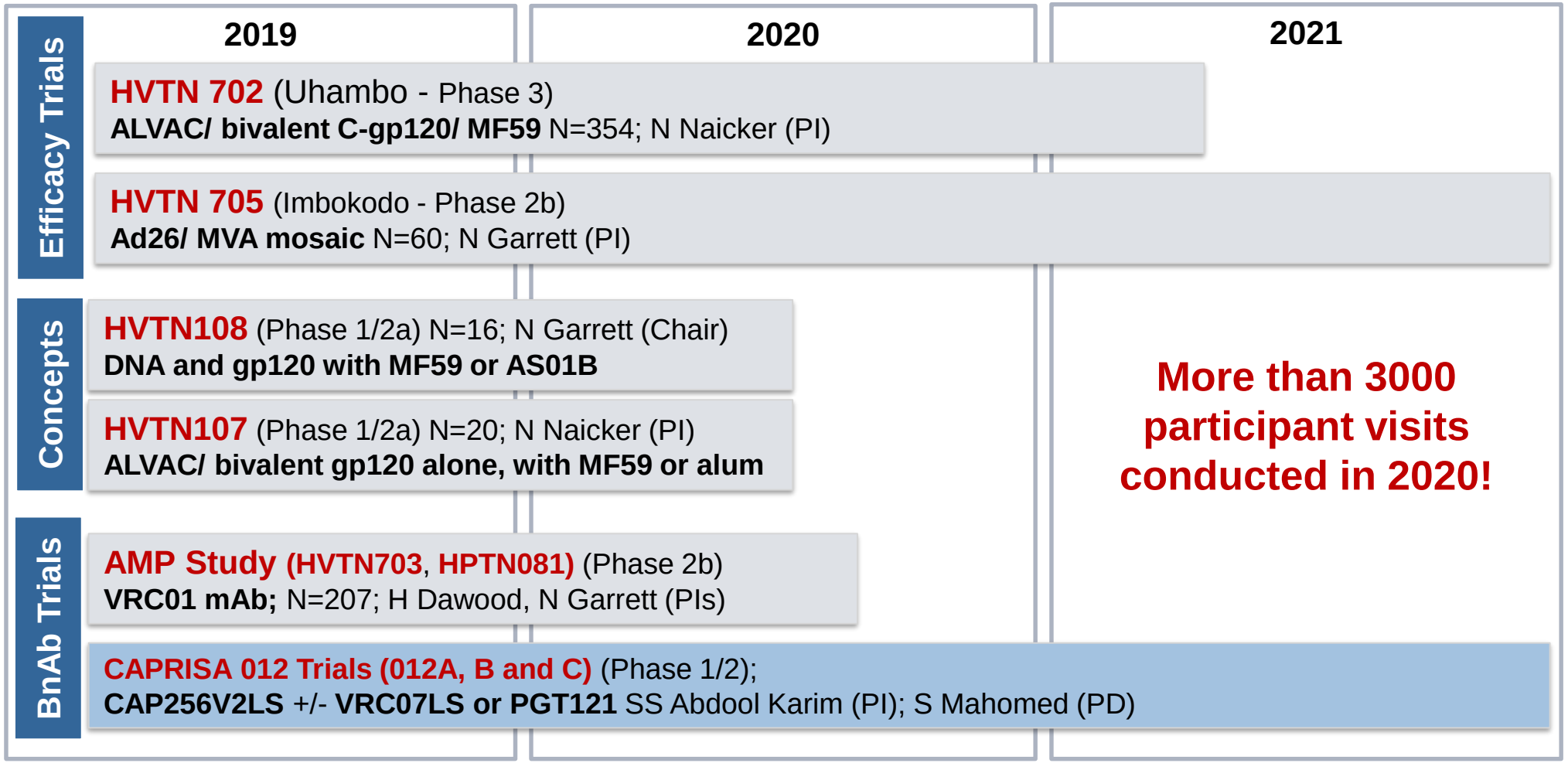


Protocol status

- First enrollment: Nov 2017
- Fully enrolled: **N=2637**
- DSMB asked to continue
- Phase 3 study (Mosaico) started among MSM and transgender in Americas

Group	N	Prime		Boost	
		M0	M3	M6	M12
1	1300	Ad26.Mos4.HIV	Ad26.Mos4.HIV	Ad26.Mos4.HIV + clade C gp140 (250 mcg + adjuvant)	Ad26.Mos4.HIV + clade C gp140 (250 mcg + adjuvant)
2	1300	Placebo			

CAPRISA HIV vaccine & broadly neutralizing antibody research



In Collaboration with the HIV Vaccine Trial Network (HVTN), National Institute of Health, US, and the EDCTP

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Antibody Mediated Prevention Phase 2b trials

- **Enrollment and follow up complete** (Total N=1,900, CAPRISA **N=207**)
- **Primary Outcomes**
  - Safety & Tolerability of VRC01 infusion
  - Efficacy to prevent HIV infection

REGIMEN	HVTN 704/HPTN 085 MSM & TG in the Americas	HVTN 703/HPTN 081 Women in sub-Saharan Africa	TOTAL	
VRC01 10 mg/kg	900	633	1533	10 infusions total - given every 8 weeks Study duration: ~22 months
VRC01 30 mg/kg	900	633	1533	
Control	900	634	1534	
Total	2700	1900	4600	

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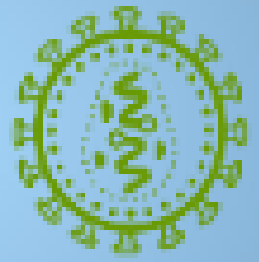
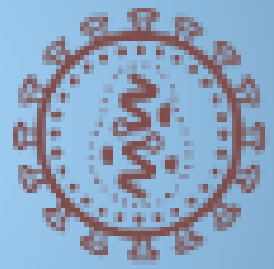
In Vitro Sensitivity to VRC01 Predicts Efficacy

- **Consistent evidence that VRC01 conferred prevention efficacy**

Against viruses measured to be neutralization **sensitive**



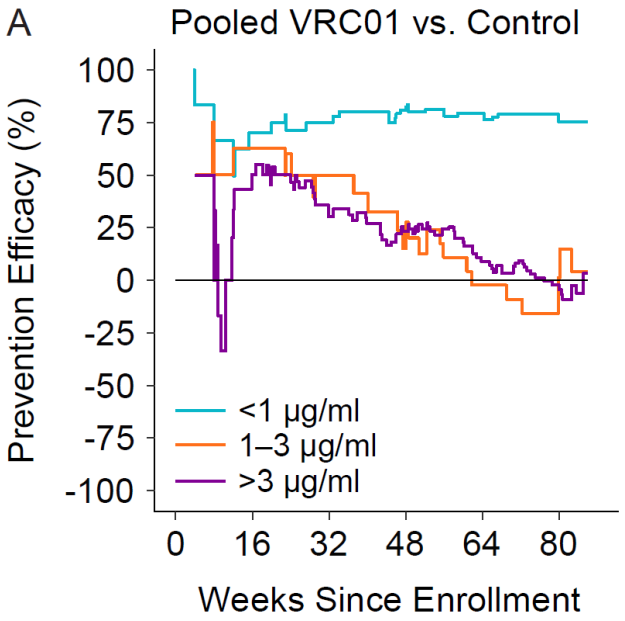
Not against viruses measured to be neutralization **resistant**



  - Monotone pattern with VRC01 protection wearing off with IC50, IC80, reciprocal of instantaneous inhibitory potential (IIP)
  - Thus, the TZM-bl target cell assay discriminates prevention efficacy

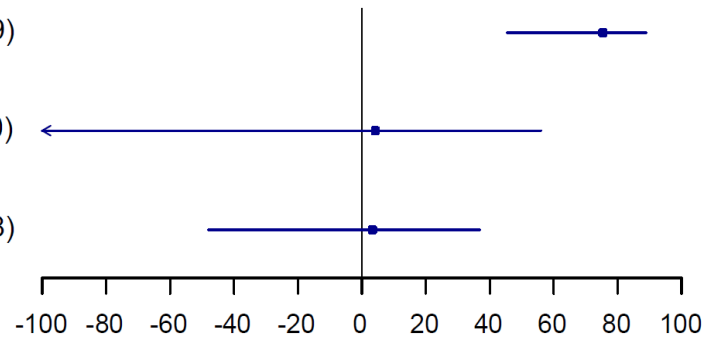
Estimated Prevention Efficacy Over Time by IC80
Efficacy Declines with IC80 Category (Pooled Trials)

A

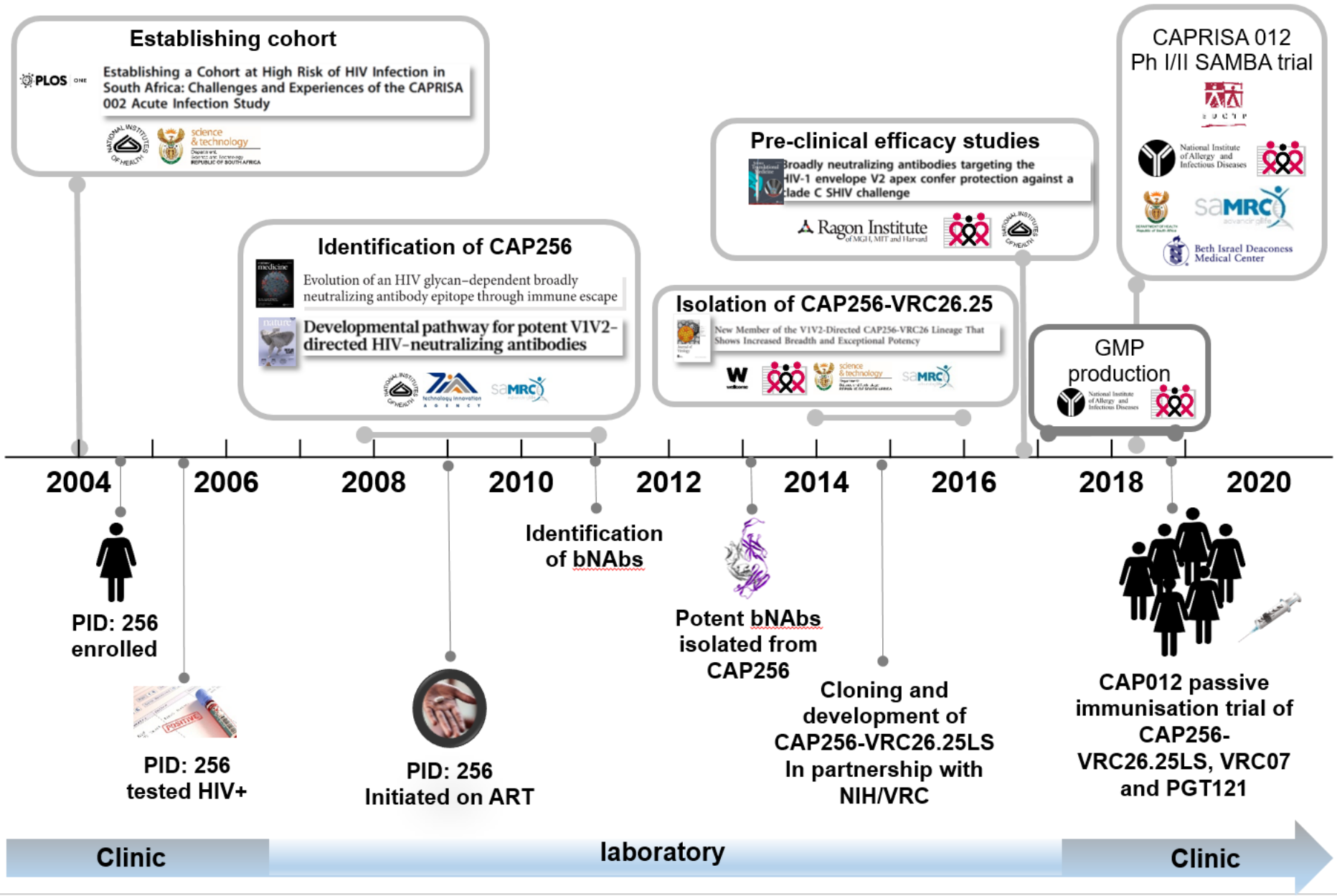


B

Pre-Specified IC_{80} Category	Treatment Arm	No. of HIV-1 Inf.	No. of Person-Years	Rate per 100 Person-Years	PE (95% CI)
<1 µg/ml	Control	19	2203	0.86	
	VRC01 Pooled	9	4427	0.20	75.4 (45.5, 88.9)
1-3 µg/ml	Control	10	2203	0.45	
	VRC01 Pooled	19	4427	0.43	4.2 (–108.7, 56.0)
>3 µg/ml	Control	35	2203	1.59	
	VRC01 Pooled	70	4427	1.58	3.3 (–48.0, 36.8)



CAP256V2LS: A long journey of discovery



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CAPRISA bnAb Programme

SAMBA: a sequence of mAb trials for HIV prevention

CAPRISA 012A: Phase I study to assess safety and PK of **VRC07-523LS** and **PGT121** administered subcutaneously in HIV-negative women

↓

CAPRISA 012B: Phase I study to assess safety and PK of **CAP256V2LS** administered subcutaneously and intravenously in HIV-negative and HIV positive women

↓

CAPRISA 012C: Phase II study to assess extended safety and PK of subcutaneously-administered **CAP256V2LS** in combination with **VRC07-523LS** and /or **CAP256V2LS** in combination **PGT121** in HIV-negative women

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CAPRISA 012A trial

BMJ Open

Assessing the safety and pharmacokinetics of the monoclonal antibodies, VRC07-523LS and PGT121 in HIV negative women in South Africa: study protocol for the CAPRISA 012A randomised controlled phase I trial

S Mahomed, N Garrett, E Capparelli, C Baxter, NY Zuma, T Gengiah, D Archary, P Moore, N Samsunder, DH Barouch, J Mascola, J Ledgerwood, L Morris, S Abdool Karim

Main objectives:

- Evaluate **safety of VRC07-523LS & PGT121** subcut
- Characterize **PK profile** of Abs
- Assess the **acceptability** of SC injections
- Concentration & **functional activity** of Abs in plasma & genital samples

Study progress:

- Study fully enrolled
- 100% Retention
- DSMB: No safety concerns
- Preliminary PK analysis completed
- Expected study end July 2020

Group	Regimen	N	Dose (mg/kg)
1	VRC07-523LS / Placebo	4/1	5 mg/kg SC one dose
2	VRC07-523LS / Placebo	4/1	10 mg/kg SC one dose
3	VRC07-523LS / Placebo	4/1	5 mg/kg SC with one repeat dose at 12 weeks
4	VRC07-523LS / Placebo	4/1	10 mg/kg SC with one repeat dose at 24 weeks
5	PGT121 / Placebo	4/1	3mg/kg SC one dose
6	PGT121 / Placebo	4/1	3mg/kg SC with one repeat dose at 12 weeks
7	VRC07-523LS + PGT121/ Placebo	4/1	5 mg/kg SC + 3mg/kg SC one dose

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CAPRISA 012B trial

First-in-human CAP256V2LS antibody trial

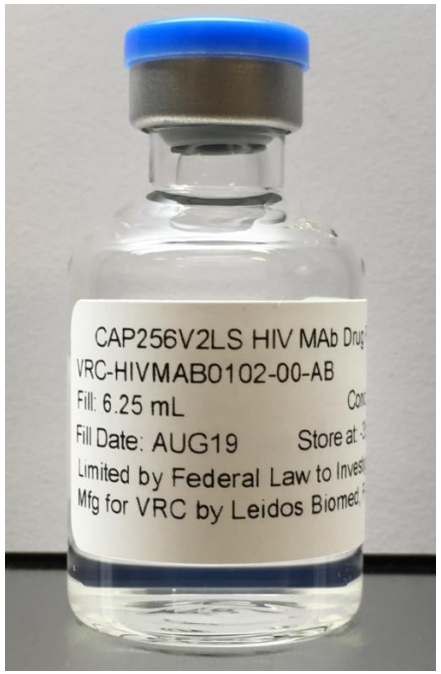
Aim:

- Determine **safety, tolerability and PK of mAb CAP256V2LS** given IV and SC to HIV positive & negative women in SA

Study update:

- Groups 1a to 3b fully enrolled
- Acceptable safety profile
- **CAPRISA 012C** with CAP256V2LS and VRC07-523LS expected to start in June 2021

Group	Participants	Regimen	N=66	Dose (mg/kg)
Group 1: Dose escalation of IV administration of CAP256V2LS				
1a	HIV negative	CAP256V2LS	4	5 mg/kg IV one dose
1b	HIV negative	CAP256V2LS	4	10 mg/kg IV one dose
1c	HIV positive	CAP256V2LS	4/2	20 mg/kg IV one dose
1d	HIV positive	CAP256V2LS	4/4	20 mg/kg IV one dose
Group 2: Dose escalation of SC administration of CAP256V2LS				
2a	HIV negative	CAP256V2LS	4	5 mg/kg SC one dose
2b	HIV negative	CAP256V2LS*	4	5 mg/kg SC one dose
2c	HIV negative	CAP256V2LS*	4	10 mg/kg SC one dose
2d	HIV negative	CAP256V2LS*	4	10 mg/kg SC with one repeat dose at 16/24 weeks[#]
2e	HIV negative	CAP256V2LS*	4	20 mg/kg SC one dose
2f	HIV negative	CAP256V2LS*	4	20 mg/kg SC with one repeat dose at 16/24 weeks[#]
Group 3: Dose escalation of the two antibody combinations				
3a	HIV negative	CAP256V2LS* + VRC07-523.LS*	4/1	10 mg/kg SC / 10 mg/kg SC one dose
3b	HIV negative	CAP256V2LS* + VRC07-523.LS*	4/1	20 mg/kg SC / 20 mg/kg SC one dose
3c	HIV negative	CAP256V2LS* + PGT121[$]	4/1	20 mg/kg SC / 5 mg/kg SC one dose
Group 4: Three antibody combination				
4a	HIV negative	CAP256V2LS* + PGT121[$] + VRC07-523.LS	4/1	20 mg/kg SC / 5 mg/kg SC / 20mg/kg SC one dose



* Higher doses will be administered with ENHANZE™ dispersing agent by Halozyme

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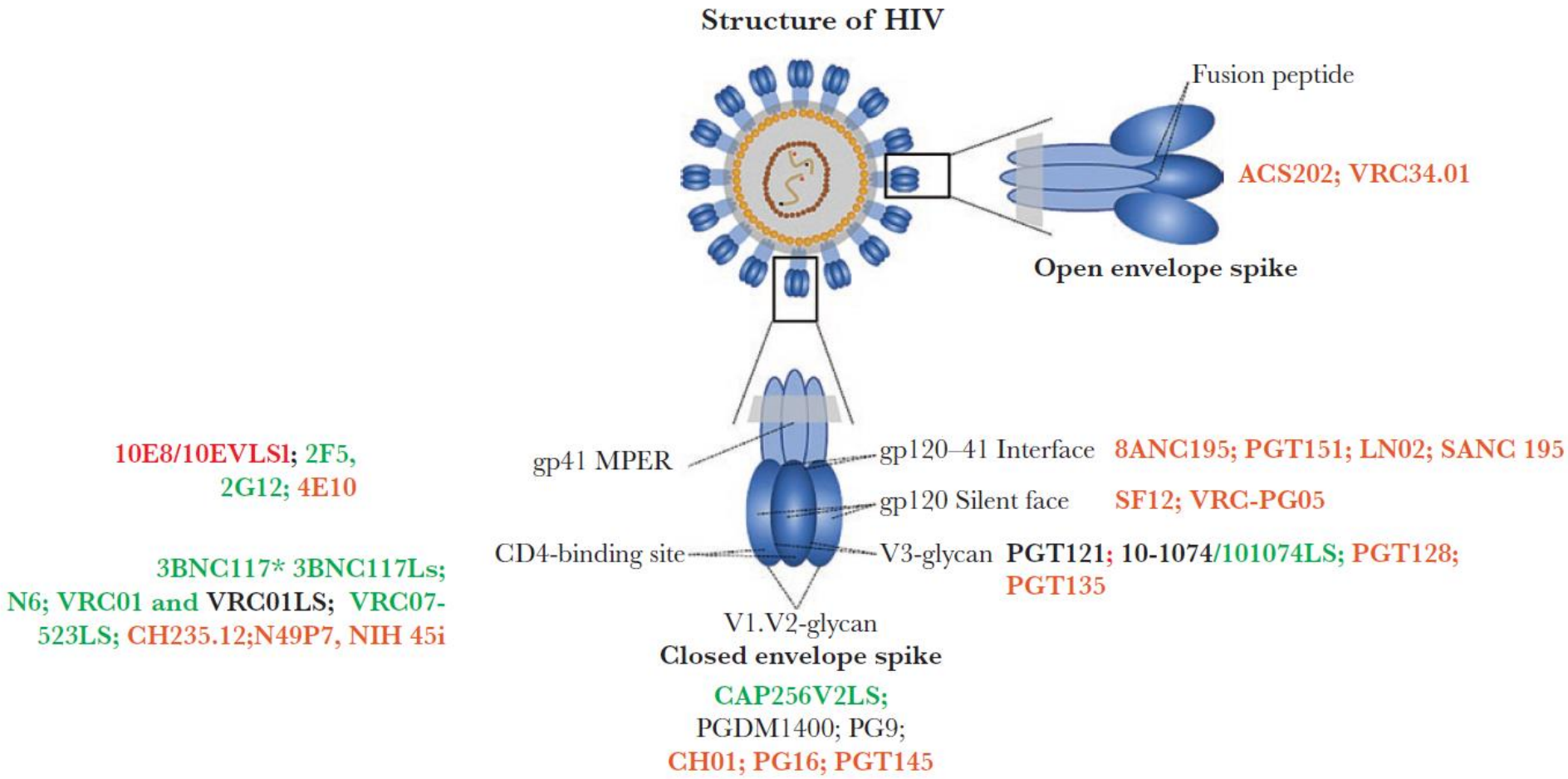
HIV–specific neutralizing antibody targets with bnAb candidates



S Mahomed, et al. Clinical Trials of Broadly Neutralizing Monoclonal Antibodies for Human Immunodeficiency Virus Prevention: A Review
The Journal of Infectious Diseases, Volume 223, Issue 3, 1 February 2021, Pages 370–380

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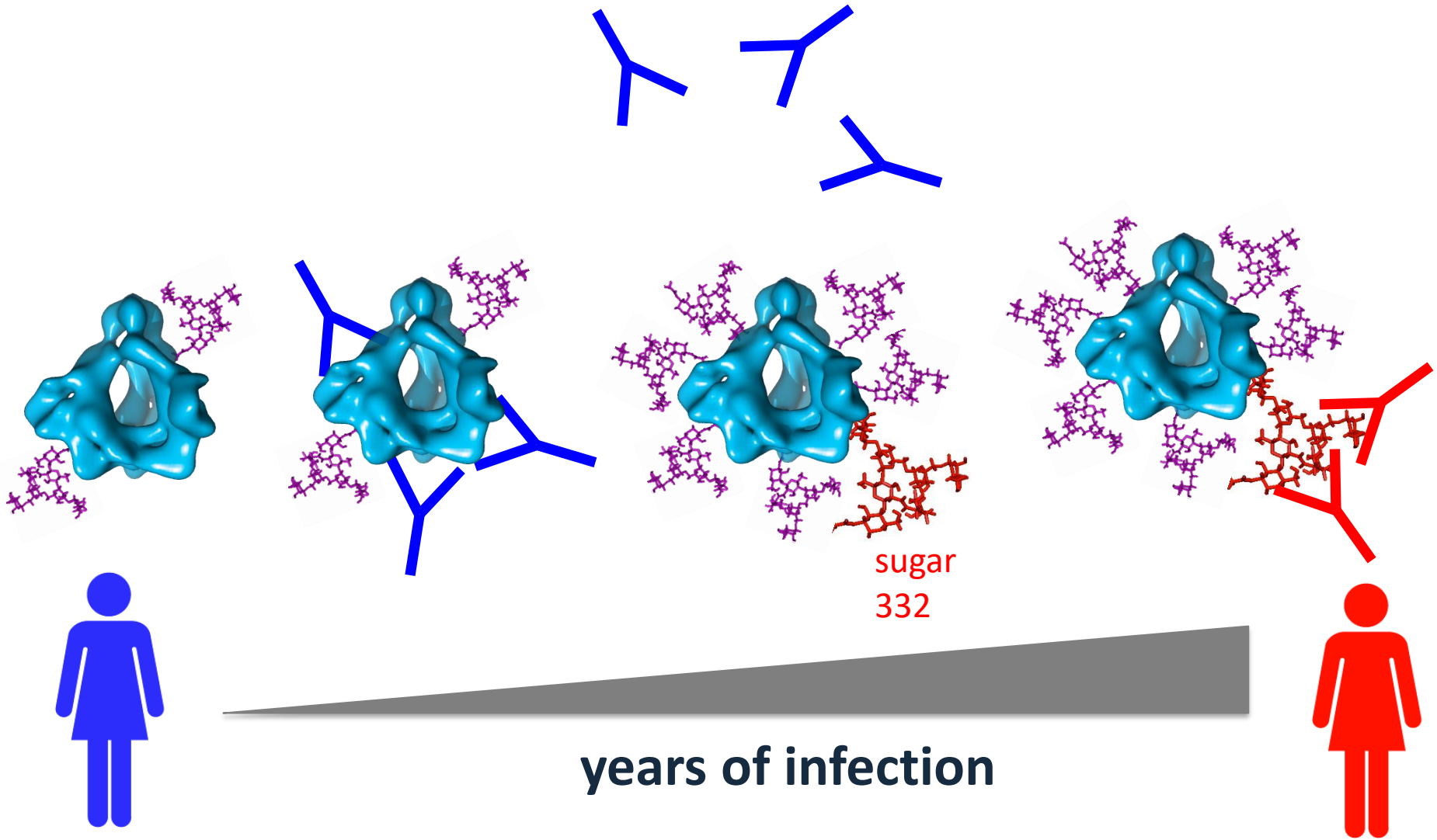
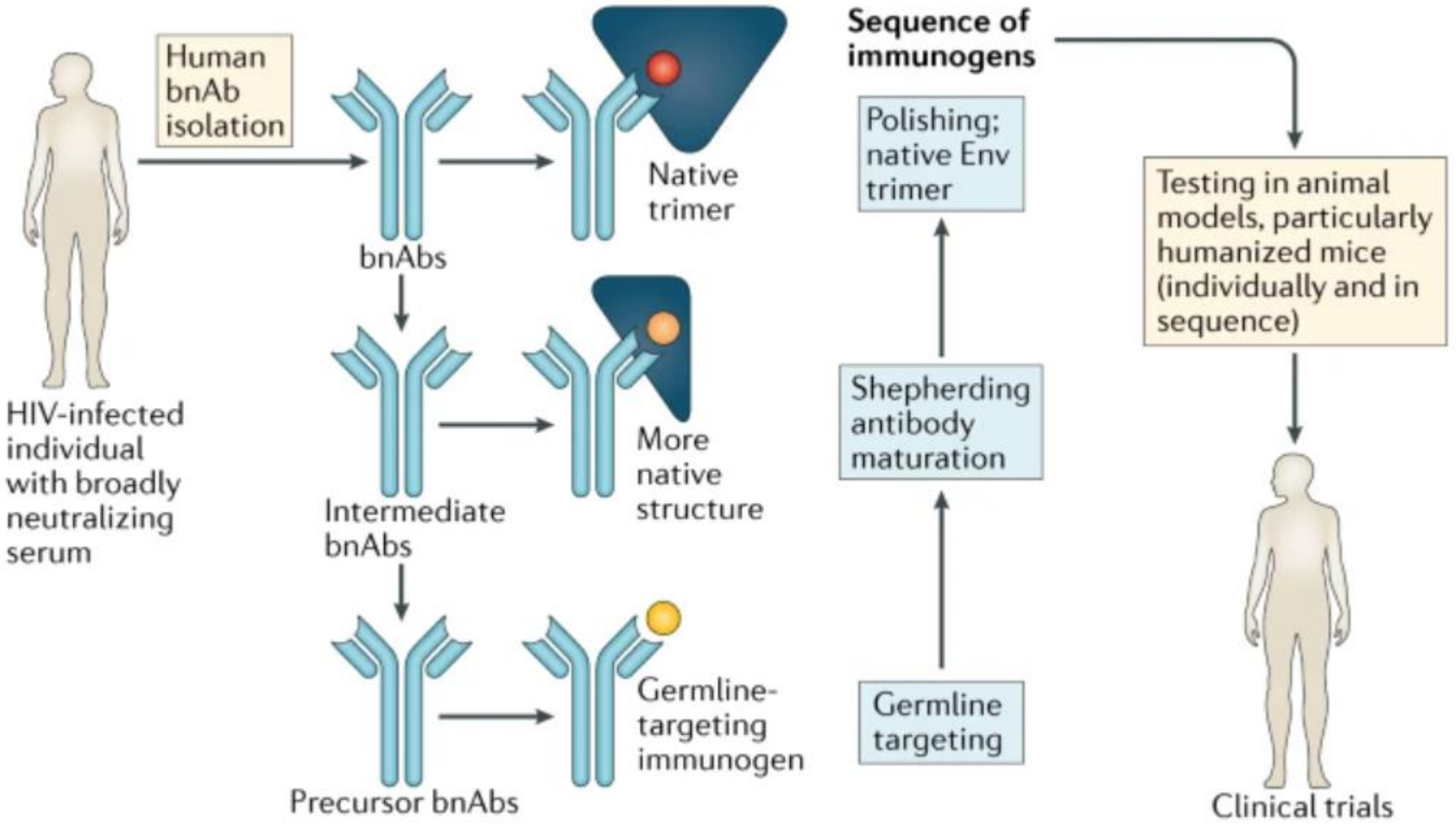
Intra-host evolution of BnAbs



Penny Moore et al. Evolution of an HIV glycan–dependent broadly neutralizing antibody epitope through immune escape. Nature Medicine volume 18, pages1688–1692(2012)

Sequential HIV vaccination strategies



Dennis R. Burton. Advancing an HIV vaccine; advancing vaccinology.
Nature Reviews Immunology volume 19, pages77–78(2019)

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CoVID-19 learned from HIV Science, can HIV field now learn from success of COVID-19 vaccines?

HIV Vaccine Approaches in COVID-19 Vaccine Development

Vaccine approaches orginally developed for HIV vaccine design are at the forefront of COVID-19 vaccine development. There are over 100 vaccine candidates in development against COVID-19, many of the vaccines and approaches in human trials have roots in HIV research. Below are some of the approaches moving forward in human trials.

Antibodies

The AMP trials, with results due in October, are now testing infusions of an HIV-neutralizing antibody every two months as a prevention method. Antibody approaches like this, including convalescent plasma, and neutralizing antibody infusions and injections, are being developed for both prevention and treatment of COVID-19.

Chimp adenovirus vector

A vaccine developed at Oxford University from a virus that infects chimpanzees is being developed for therapeutic and preventive clinical trials against HIV and a number of other diseases. That chimpanzee virus platform has been adapted as a COVID-19 vaccine candidate and is now in clinical trials.

DNA

HIV vaccine approaches using a DNA platform are now being explored for COVID-19. Inovio has begun testing its DNA vaccine platform, originally developed for HIV vaccines, for use as a COVID-19 vaccine.

Human adenovirus vectors

Multiple adenovirus subtypes have been developed as HIV vaccine candidates, most notably, Janssen's Ad26 candidate, which is now in two large HIV vaccine efficacy trials. Janssen is now adapting its Ad26 as a COVID-19 vaccine. There are also several other adeno-based COVID-19 vaccines in development, such as the Ad5 adenovirus being tested by the Chinese military.

mRNA

Messenger RNA (mRNA) vaccines, potentially more potent than DNA platforms, have been developed as HIV vaccine candidates. Now, several mRNA vaccine candidates against COVID-19 are in clinical trials sponsored by Moderna, CureVac and Pfizer/BioNTech.

AVAC 25 Years and Counting

May, 18 2020

avac.org

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Unique Challenges to HIV Vaccines

- **HIV attacks CD4+ T-cells thereby weakening the conductors of the immune system in clearing the infection**
- **Continuously mutates and recombines resulting in an extensive diversity of viral strains**
- **No good model of natural clearance of infection prevents discovery of correlates of protection**
- **This is the era of new vaccine concepts (see example of mRNA vaccines for the prevention of COVID-19**

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Conclusions

- **CAPRISA likes the MRC and are looking forward to working with you over the coming years.**
- **HIV Vaccine research has had its ups and downs but we are eagerly awaiting the Ad26 mosaic vaccine results**
- **Everyone talks about broadly neutralizing antibodies, but combinations will be required to prevent infection.**
- **We may require sequential vaccinations to shepard the immune system to make them.**

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Acknowledgements

Investigators

- **Nivashnee Naicker and Sharana Mahomed**
- **Salim & Quarraisha Abdool Karim** and the CAPRISA study teams
- **Lynn Morris, Penny Moore** and the Neutralizing Antibody team **(NICD)**
- **Carolyn Williamson, Melissa-Rose Abrahams** & Viral Diversity team **(UCT)**
- **Wendy Burgers** and the Cellular Immunity teams **(UCT)**
- **Jo-Ann Passmore** and the Mucosal Immunology team **(CAPRISA, UCT)**
- **Natasha Samsunder and the Laboratory and Support teams (CAPRISA)**

Vaccine & Pathogenesis Team

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EDCTP European & Developing Countries Clinical Trials Partnership
HIV VACCINE TRIALS NETWORK
NATIONAL INSTITUTES OF HEALTH
HPTN HIV Prevention Trials Network
NRF National Research Foundation
science & technology Department: Science and Technology REPUBLIC OF SOUTH AFRICA
saMRC advancinglife
health Department: Health REPUBLIC OF SOUTH AFRICA
CAPRISA CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA